REMARKS

Reconsideration of the rejection of all claims is respectfully requested in view of the above amendments and the following remarks.

Claim Amendments

Claims 33-38, which were newly presented with the previous Amendment and Response, have been designated as withdrawn, pending allowance of a generic claim.

Elections/Restrictions

Pursuant to the Examiner's request for a single species, Applicants provisionally elected fenofibrate as the specific "second drug" species, and provisionally elected the species where the first and second drugs are administered together. In accordance with the provisional nature of the species election, Applicants have maintained claims 7-10 and 13-15 as withdrawn, so that the subject matter is available for examination as soon as the elected subject matter is found to be patentable.

In the Amendment and Response filed March 10, 2004, applicants added new claims 33-38, which are all dependent on one or more of the provisionally elected claims. However, the Examiner has asserted that these newly submitted claims are directed to an invention that is independent or distinct from the invention originally claimed, characterizing the claims as encompassing "a kit which has separate components from the claimed combination and a method of using the claimed combination, which can be used in different methods such as treating wounds." The basis for this assertion and characterization of these claims is not understood.

Elected claim 1 is directed toward a non-interacting drug combination, which includes as a first drug, an HMG-CoA reductase inhibitor and, as a second drug, an inhibitor, inducer or substrate of P450 isoenzyme 3A4. According to the provisionally elected species, the second drug is fenofibrate. New dependent claims 33-38 are simply dependent variations of the non-interacting drug combination of elected claim 1:

- In new claim 33, the first and second drugs of claim 1 are simply present in a pharmacy pack as separate dosage forms, and it is not seen how an independent claim, limiting the drug combination of claim 1 to a particular form, constitutes an independent or distinct invention.
- New claim 34 is directed to a method of treating hypercholesterolemia or mixed hyperlipidemia by administering an effective amount of a pharmaceutical formulation of elected claim 12 (which is a formulation comprising the non-interacting drug combination of claim 1 together with a pharmaceutically acceptable diluent, carrier or adjuvant.
- New claim 35 is directed to the treatment of hypercholesterolemia or mixed hyperlipidemia by administering an effective amount of the first drug and an effective amount of the second drug as claimed in elected claim 1, as separate dosage forms. Again, once the drug combination of claim 1 is allowed, it is believed appropriate to rejoin methods of using such drug combination in the same application.
- New claims 36 and 37 simply further refine the method of claim 35 with respect to whether the first and second drugs are administered simultaneously or sequentially. Again, is believed appropriate to rejoin these method claims with the drug combination claims upon which they are dependent.

In view of the Examiner's position and the above observations, claims 33-38 have been designated as "withdrawn" in the above amendments, rather than canceled, so as to be available for rejoinder upon allowance of the base drug combination claims.

Claimed Rejections-35 USC §103

Claims 1, 2, 4-6 and 12 have been rejected under 35 USC §103(a) as being unpatentable over Curtet et al, EP 96400133, JP 401254624 or JP 405194209 taken with EP 521471, Liao et al. or WO 99/22728. The Examiner asserts that since the references each teach that the individual components of the composition are known in the art to be used for

the same purpose, then it is obvious to combine them into a single combination. In support of this assertion, the Examiner cites several legal references for the proposition that it is well known that it is *prima facie* obvious to combine two or more ingredients, each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition which is useful for the same purpose. In response to this same rejection, Applicants' Amendment and Response of March 10, 2004, presented substantial literature and other evidence to support their argument that persons skilled in the art at the time of the invention were taught away from making the combination now claimed, because of the well known detrimental drug interaction between HMG-CoA redactase inhibitors and a second drug that is an inhibitor, inducer or substrate of P450 isoenzyme 3A4, such as fenofibrate (the presently provisionally elected second drug species).

In order to make out a case of *prima facie* obviousness from a combination of references, the Examiner must find some suggestion or motivation to combine the reference teachings at the time of applicants' invention, and must show that there would have been a reasonable expectation of success. Both the teaching or suggestion to make the combination and the reasonable expectation of success must be found in the prior art, and not based on a hindsight application of applicants' disclosure.

Generalizations can be made from certain relationships such as homologues, positional isomers, and the combination of ingredients separately known to be useful for the same purpose, which may create a presumption of the necessary suggestion or motivation, and of a reasonable expectation of success, to support an initial assertion of *prima facie* obviousness. However, when such a generalization is used in place of an actual teaching in the art, the circumstances of each case must be evaluated to see whether the generalization is applicable to those particular circumstances. Where the particular circumstances demonstrate that the generalization is not appropriate, then the initial assertion of prima facie obviousness must be withdrawn. The Federal Circuit has caution against using such generalizations as giving rise to prima facie obviousness (in context of a case involving chemical structure) in *In re Grabiak*, 226 USPQ 870 (Fed. Cir. 1985):

> Analysis of those circumstances in which a prima facie case has or has not been made in view of the degree of structural similarity or

> dissimilarity, or the presence or absence of similar utility between the prior art compound and that of the applicant, has inspired generations of applicants, courts, and scholars. Upon review of this history, we have concluded that generalization should be avoided insofar as specific chemical structures are alleged to be prima facie obvious one from the other.

226 USPQ at 871-72 (emphasis added). While the case before the Court in *Grabiak* involved generalizations concerning chemical structure, the caution is believed to be equally applicable to the use of generalizations as giving rise to *prima facie* obviousness in all arts.

Moreover, the determination of *prima facie* obviousness is only a preliminary step in an obviousness determination -- just a starting point and not the end of the issue. In particular, factors or evidence that would lead persons skilled in the art away from making such a combination, evidence of unexpected results from making such a combination, and any other relevant factors must all be considered together and as a whole in reaching the ultimate conclusion of whether Applicants' claimed invention is or is not obvious over the asserted combination of references.

However, it appears from the current Action that the Examiner is inappropriately treating his assertion of *prima facie* obviousness, arising only from this *generalization*, as being a final, irrefutable conclusion of obviousness, as evidenced by the paragraph bridging pages three and four of the current Action:

> The law is clear and so is this rejection. Speculation by the applicant and others may have been at one time but it was clear that the components were each known individually in the art to be used for the same purpose. Thus, by definition, it is obvious to combine them into one composition to be used to treat the same purpose as before they were combined.

Applicants respectfully disagree with this position of the Examiner, in that it inappropriately diminishes, and thus effectively ignores, the evidence submitted by Applicants of knowledge in the art at the time of their invention, and treats *prima facie* obviousness as being a final, irrefutable conclusion, rather than just a rebuttable starting point.

The Examiner's attention is respectfully again drawn to the evidence presented at pages 10 through 14 of Applicants' March 10, 2004 response, which establishes that persons of ordinary skill in this art would have been well aware, through the literature and/or

otherwise, that there was a serious risk of interaction between HMG-CoA reductase inhibitors and certain second drugs such as fibrates, and that this interaction could impair the metabolism of a staten or the other drug such that high concentrations and toxic levels of drugs could result. This is not "speculation by applicant and others may have been at one time", but rather it is based on substantial literature references in the field prior to and at the time of Applicants' invention.

The case law is clear that the Examiner cannot simply ignore or push aside such evidence. Moreover, it is well settled that a *prima facie* case of obviousness can be overcome by evidence showing that the generalization which was the basis of *prima facie* obviousness is not applicable to the particular circumstances of Applicants' claims. Thus, even if it would have been *prima facie* obvious to combine the two types of drugs that were individually known to lower cholesterol, it is respectfully submitted that the literature evidence presented by Applicants, and not refuted by the Examiner, overcomes that generalization with respect to the particular combination as presently claimed.

Accordingly, any case of *prima facie* obviousness that might arise out of the generalizations noted in the case law cited by the Examiner is just that, *prima facie*, a first impression or preliminary position. However, when the generalization giving rise to the asserted *prima facie* obviousness in considered in light of the contrary actual evidence that Applicants have presented on the particular circumstances of the combination presently claimed, it is respectfully submitted that any such *prima facie* obviousness has been overcome.

Applicants do not presently contest that *a prima facie* case of obviousness can arise from the simple combination of two compositions, each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose. This concept is set forth in the MPEP in §2144.07 citing, *inter alia,* in *In re Kerkhoven,* 626 F.2d 846, 850, 205 USPQ 1069, 1072 (CCPA 1980), and *In re Crockett,* 279 F.2d 274, 126 USPQ 186 (CCPA 1960). However, it is clear from these cases and other legal guidance discussed below that while this generalization may support an initial assertion of *prima facie* obviousness, all relevant evidence and circumstances (including that put forward

by Applicants) must be considered as a whole before reaching an ultimate conclusion on the obviousness issue.

The legal concept of *prima facie* obviousness is discussed in the MPEP beginning at §2142. It is there stated:

> The legal concept of *prima facie* obviousness is a procedural tool of examination which applies broadly to all arts. It allocates who has the burden of going forward with production of evidence in each step of the examination process [Citations omitted]. The examiner bears the initial burden of factually supporting any *prima facie* conclusion of obviousness. If the examiner does not produce a *prima facie* case, the applicant is under no obligation to submit evidence of nonobviousness.

This section continues:

> To reach a proper determination under 35 U.S.C. 103, the examiner must step backward in time and into the shoes worn by the hypothetical "person of ordinary skill in the art" when the invention was unknown and just before it was made. In view of all of the factual information, the examiner must then make a determination whether the claimed invention "as a whole" would have been obvious at that time to that person. Knowledge of applicant's disclosure must be put aside in reaching this determination, yet kept in mind in order to determine the "differences," conduct the search and evaluate the "subject matter as a whole" of the invention.

The next portion of this MPEP §2142 discusses the requirements for establishing a *prima facie* case of obviousness:

> To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all of the claim limitations. The teaching or suggestion to make the claimed invention and the reasonable expectation of success must both be found in the prior art, and not based on applicant's disclosure. *In re Vaceck,* 947 F.2d 488, 20 USPQ2d 1438 (Fed.Cir. 1991).

* * * * *

> If the examiner determines there is factual support for rejecting the claimed invention under 35 U.S.C. 103, the examiner must then consider any evidence supporting the patentability of the claimed invention, such as any evidence in the specification or any other evidence submitted by the applicant. The ultimate determination of patentability is based on the entire record, by a preponderance of evidence, with due consideration to the persuasiveness of any arguments and any secondary evidence.
>
> * * * * *
>
> When an applicant submits evidence, whether in the specification as originally filed or in reply to a rejection, the examiner must consider the patentability of the claimed invention. The decision on patentability must be made based upon consideration of the evidence, including the evidence submitted by the Examiner and the evidence submitted by the applicant. A decision to make or maintain a rejection in the face of all the evidence must show that it was based on the totality of the evidence. Facts established by rebuttal evidence must be evaluated along with the facts on which the conclusion of obviousness was reached, not against the conclusion itself. *In re Eli Lilly & Co.*, 902 F.2d 943, 14 USPQ2d 1714 (Fed. Cir. 1990).

(MPEP §2142; emphasis added).

In view of the foregoing discussion of the case law applicable to *prima facie* obviousness, and the interpretation thereof by the U.S. Patent and Trademark Office in the MPEP, it should be clear that a determination of *prima facie* obviousness, particularly if based only on a generalization such as here, is only the beginning of an obviousness evaluation, and not the end. In any event, *all evidence* related to the obviousness issue, particularly including evidence submitted by applicant, *must* be given full consideration *together with* all other evidence or factors bearing on obviousness, before reaching an ultimate conclusion on the obviousness issue.

However, contrary to this established law, the Examiner has applied the generalization (that a combination of two or more ingredients, each separately taught to be useful for the same purpose, may give rise to *prima facie* obviousness) as a final, irrebuttable conclusion of obviousness, and therefore did not give proper consideration to Applicants' previously submitted evidence.

It is therefore respectfully requested that the Examiner withdraw the finality of this Action, and give full and fair consideration to that evidence. Additionally, in view of the Examiner's comment, essentially dismissing Applicants' argument presented in the previous response,[1] submitted herewith, in further and broader support of Applicants' argument are several additional literature references which also show prior recognition in the art that HMG-CoA reductase inhibitors (statins) could produce dangerous drug interactions. These references are follow:

Herman, CMAJ, Nov. 16, 1999, 161(10); pp. 1281-1286
Corsini et al., Pharmacology & Therapeutics, 84 (1999) pp. 413-428

Kantola et al., Eur J Clin Pharmacol (1999), 54: pp. 851-855

Michalets, Pharmacotherapy, 1998, 18(1), pp. 84-112

Zhao et al., Eur. J. Drug Metab. Pharmacokinet., 1999, Vol. 24, No. 3, pp. 272-278

Neuvonen et al., Clincal Pharmacology & Therapeutics, Vol. 63, No. 3, March 1998, pp. 332-341

It is respectfully submitted that these additional literature references should overcome the Examiner's characterization of "supposedly" with respect to the state of knowledge in the art at around the time of Applicants' invention.

In view of the foregoing observations, arguments and supporting case law, it is believe that the Examiner's ground for rejection have been fully addressed and overcome. Withdrawal of this rejection is therefore believed to be in order, and is respectfully requested, together with rejoinder of the provisionally non-elected claims for consideration and allowance in this application.

EXCEPT for issue fees payable under 37 C.F.R. § 1.18, the Director is hereby authorized by this paper to charge any additional fees during the entire pendency of this

[1] Comment at page 3 of the Action, that "Applicants argue that the individual components are allegedly not obvious to combine together because they supposedly would have [had] negative effects on the body . . ."

application including fees due under 37 C.F.R. §§ 1.16 and 1.17 which may be required, including any required extension of time fees, or credit any overpayment to Deposit Account 50-0310. This paragraph is intended to be a **CONSTRUCTIVE PETITION FOR EXTENSION OF TIME** in accordance with 37 C.F.R. § 1.136(a)(3).

Respectfully Submitted,
Morgan Lewis & Bockius LLP

Date: November 1, 2004 By: _____

Morgan Lewis & Bockius LLP
Customer No. **09629**
1111 Pennsylvania Avenue, N.W.
Washington, D.C. 20004
Tel. No.: 202-739-3000
DJB:mk

Donald J. Bird
Registration No. 25,323
Tel. No.: (202) 739-5320
Fax No.: (202) 739-3001